Victim w/ ext (i) #6
JL 5-16.03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Art Unit: 1642
NIELSEN, et al.	)	Examiner: UNGAR, S.
Serial No.: 09/922,718	)	Washington, D.C.
Filed: August 7, 2001	)	May 12, 2003
For: PAI-1 DETERMINATION AND USE THEREOF	)	Docket No.: NIELSEN=2D

ELECTION WITH TRAVERSE

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

S i r :

1. In response to the restriction mailed March 11, 2003, Applicant's hereby make the following elections:

(1) within groups 1-96, Applicants elect the group corresponding to determination of variable (4)[1] alone by means of marker (i)

(2) within groups 97-121, Applicants elect group 99 (colon tumor).

(3) within groups 122-142, Applicants elect group 135 (prognosis of individual having a malignant tumor).

(4) for species election (A), Applicants elect that the sample be "tumor tissue".

(5) for species election (B), Applicants elect that the assay format be an immunoassay.

(6) for species election (C), Applicants elect the antibody secreted by clone 1.

2. It is noted that the reference to "Inventions III-VII" on page 9, line 8 of the office action is not understood.

3. The Group-level restrictions are respectfully traversed for the reasons set forth below.

The purpose of restriction practice is to prevent subversion

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[1] the likely progression of a malignant tumor in a subject.

of the statutory fee structure and to preserve the integrity of the system of examination and classification. Chisum, Patents §12.01. However, restriction practice must strike a balance between the needs of the PTO and those of the Applicant. A properly written specification will disclose an invention both generically and specifically, setting forth alternatives where appropriate. An applicant should not be penalized for so detailing his or her invention by using restriction practice to fragment the claimed invention into so many small pieces that it would be uneconomical for the applicant to protect his whole invention by filing the indicated number of divisional applications.

Even at the group level, Applicants are required to elect one of 96 groups, then one of 26 groups[2], and then one of 21 groups. The implication is that to cover Applicants' invention as claimed, Applicants would have to file 96x26x21=52,416 applications! This seems inequitable given the clear relationship of the embodiments in question.

There are two criteria for restriction:

(A) the inventions must be independent or distinct, and

(B) there must be a serious burden on the examiner if restriction is not required. MPEP §803.01.

The restriction is utterly devoid of analysis of its compliance with these criteria. The Examiner may use "factorial analysis" as a step in identifying the distinct invention, but the analysis must be justified by relating the choice of factors, and the choice of possible value for each factor, to the legal standard. There is no such justification here; the Examiner simply assumes distinctness. This is contrary to the requirements of MPEP §816.

Likewise, there is no burden analysis (i.e., "reasons for insisting on restriction"), see MPEP §817, "Outline of Letter", (D), or even (for groups 1-96) identification of the

[2] There is a group "111a".

classification of each group as required by MPEP §808.02.

Consequently, the restriction is procedurally defective and should be vacated even without consideration of the merits. However, in the interest of expediting prosecution, we will address the merits to the extent possible at this time.

Distinctness

Claims 1-43 and 51-69 are cancer diagnostic method claims. Claims 44-50 are assay claims which recite the same but which do not specify a clinical purpose. Clearly they are at least drawn to "related inventions". Hence, the issue is whether the inventions are distinct. See MPEP §806.05.

"In applications claiming inventions in different statutory categories, only one way distinctness" is generally needed to support a restriction requirement". MPEP §806.05(e). But all of these claims belong to the same statutory class as defined by 35 USC §101, i.e., they are all "process" claims.

The implication of MPEP §806.05(e) is that, for inventions in the same category, "two-way distinctness" is required for restriction. That is in fact the rule applied by MPEP §806.05(c) to combination/subcombination claiming.

We turn now to consider groups 1-96. The "factorial analysis" is based on claim 1:

> 1. A screening method for better ascertaining at least one variable selected from the group consisting of (1) the likelihood of the presence of a tumor in a subject suspected of having a tumor, (2) the likelihood of the presence of a malignant tumor in a subject suspected of having a malignant tumor (3) the likelihood of the presence of a tumor metastasis in a subject suspected of having a tumor metastasis, and (4) the likely progression of a malignant tumor in a subject, the method comprising
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> (a) determining the level of a marker, selected from the group consisting of (i) PAI-1 protein abundance, (ii) uPA:PAI complex abundance (iii) the change in PAI-1 protein abundance over time, and (iv) the

change in uPA:PAI complex abundance over time, in a test sample, and, in the case of (iii) and (iv) above, over a plurality of test samples taken at different times,

said test sample or samples being of or derived from a body fluid or tissue of said subject,

said tumor being of a kind such that there is a correlation between the level of said marker and at least one of variables (1)-(4) above, and

(b) correlating the level of said marker for said sample or samples, and the reference level of said marker for a corresponding reference sample or samples,

whereby at least one of variables (1)-(4) is better ascertained.

There plainly is a very close relationship among the four "variables". Variable #1 is determining if the subject has a tumor at all. Variable #2 is determining if the tumor is malignant. Variable #3 is determining if the tumor (presumably malignant) is likely to metastasize. Finally, variable #4 is determining the likely "progression of a malignant tumor", which presumably encompass both metastasis and in situ growth of the primary tumor.

While these variables might not be identical, they may be highly correlated. Variable (3) seems to be a subset of variable (4), for example.

The choice of variable affects how the assay is carried out only in the final "correlation" step, where the marker level is interpreted. The differences between a variable (2) assay and a variable (3) assay might be just the reference level.

We think it very improbable that a restriction among variables (1)-(4) will satisfy the "two-way" distinctness test.

Even if assays for these four variables were considered distinct, it does not follow that assays for one of the variables are distinct from assays for two, three or all four of the

variables (the 4!=24 in the Examiner's factorial analysis).

The relationship of a single variable assay to a two variable assay is clearly a subcombination/combination one, and MPEP 806.05(c) applies. In our opinion, criterion (A) is not satisfied; the combination does require the particulars of the subcombination for patentability. Turning to the markers, there arguably is a subcombination/combination relationship between (i) and (iii), and between (ii) and (iv). That is because determining the change necessarily requires determining the abundance on at least two occasions. At this moment, we are not prepared to say whether or not criteria (A) and (B) of MPEP 806.05(c) are satisfied. We would like to see the Examiner's position on this first. For example, the Examiner could take the position that if high PAI-1 is bad, that an increase in PAI-1 over time is obviously bad. In that case distinctness is lacking. Or we could find that for one of the variables, there is a better correlation with the change in PAI-1 than with the raw value. If so, then there is an argument for distinctness. It may be better to rejoin the groups and make the restriction only if Applicants argues for their distinctness in order to overcome a prior art rejection.

With regard to (i) the PAI protein and (ii) the complex, the onus is on the Examiner to show two-way distinctness.

Turning to groups 97-109, these differentiate the invention on the basis of the nature of the tumor, e.g.; breast, gastric, etc. In our experience, restrictions of this type are usually species restrictions. It is noted that we have generically claimed assaying all tumors in a single claim. Hence, it does not appear proper to treat these as separate group-level inventions. Rather Applicants should have the opportunity to establish that a generic claim is allowable.

Groups 110-121 do not seem to be related to 97-109, despite the wording of the restriction. Most of them appear to cover the same inventions as those set forth in 1-96. For example, what

is the difference between group 111a, and the group within 1-96 combining variable (2) and marker (i)?

Certain of the groups set forth PAI-1 DNA and RNA as markers. There is a plain relationship between the mRNA level and the protein level; absence the showing of an unsuspected difference, these are not distinct. So arguably the RNA marker should be joined with the protein marker. However, we would be willing to accede to the DNA and RNA being restricted from the protein if the restriction were reduced as proposed below.

Again, the combination groups (112-114, 115-121) must be compared with the subcombination groups (110, 111, 111a, 116, 117) according to combination/subcombination restriction practice.

Vis-a-vis the distinction between detecting "presence" and detecting "progression", please see our comments on variables (1)-(4) in groups 1-96.

Turning to groups 122-140, these seem to raise issues similar to those already addressed (i.e., location of tumor, presence vs. progression vs. prognosis).

Finally, we come to groups 141 and 142. Plainly, there is a subcombination/combination relationship of 141 to 142. Moreover, 141 has a subcombination/combination relationship to the clinical claims of groups 1-96 in which the marker is (i), and 142 to those in which both markers (i) and (iii) are used.

Burden

The Examiner has not specified classification for groups 1-96. For the other groups, we find the following:

Class/Subclass[3]	Groups
435/7.1	105-109, 113-115, 119-121, 139-142
435/6	110-112, 113-115, 116-118, 119-121
435/4	113-115, 119-121, 139-142
435/4+ (includes 4, 6, 7.1)	122-138

Even if we take this classification at face value, it is hard to consider this evidence of separate classification. All of the claims are classified into no more than three subclasses. Some claims are placed in more than one of these subclasses. There seem to be some arbitrariness as to which subclass a claim is assigned to. For example, group 105 is assigned to 435/7.1 even though it is not antibody-specific. Should it not be in 435/4?

We suggest revising the restriction by replacing groups 1-142 with at most a 3-way restriction as follows:

(I) assays for PAI-1 protein (435/4)

(II) assays for PAI-1 DNA or mRNA (nucleic acid per 435/6)

(III) assays for uPA:PAI complex (435/4)

This presumes that the Examiner can demonstrate two-way distinctness, and that it would be burdensome to search all three. Arguably, (I) and (III) should still be joined because they are commonly classified.

We would not object in principle to a <u>species</u> restriction based on the tumor type, except that we will of course take the position that the species restriction should be withdrawn because

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[3] 435/4
MEASURING OF TESTING PROCESS INVOLVING ENZYMES OR MICROORGANISMS; COMPOSITION OR TEST-STRIP THEREFORE; PROCESSES OF FORMING SUCH COMPOSITION OR TEST STRIP
435/6 (indented under 435/4)
involving nucleic acid
435/7.1 (indented under 435.4)
involving antigen-antibody binding, specific binding protein assay or specific ligand-receptor binding assay

generic claims are allowable.

4. Species Restriction

Species election (A) violates MPEP §806.04(f) which requires that species be defined by "mutually exclusive characteristics". "Frozen tumor tissue", "unfixed tumor tissue", and "malignant tissue", and possibly also "extracts of tumor tissue", are all subsets of "tumor tissue".

We would suggest revising (A) to require election of

-tumor tissue (including cells) and extracts

-normal tissue (including cells) and extracts

-body fluids.

Respectfully submitted,

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